

We claim:

1. Valacyclovir hydrochloride form I.
2. Valacyclovir hydrochloride form I of claim 1 characterized by x-ray diffraction reflections at about 3.7°, 8.6°, 10.6°, 10.9°, 16.5°, 24.0° and 27.2° $\pm 0.2^\circ$ 2 θ .
- 5 3. Valacyclovir hydrochloride form I of claim 2 further characterized by x-ray diffraction reflections at about 9.5°, 10.9°, 20.1°, 21.4°, and 26.7° $\pm 0.2^\circ$ 2 θ .
4. Valacyclovir hydrochloride form I of claim 2 further characterized as having a weight loss of between about 6% and about 9% as measured by thermogravimetric analysis over the temperature range between about 25°C and about 125°C.
- 10 5. Valacyclovir hydrochloride in form I of claim 1 characterized by the x-ray diffraction pattern substantially as shown in figure 1.
6. Valacyclovir hydrochloride sesquihydrate.
7. Valacyclovir hydrochloride form II.
8. Valacyclovir hydrochloride form II of claim 7 characterized by x-ray diffraction
15 reflections at about 6.6°, 19.0°, 21.5°, 27.4°, and 28.5° $\pm 0.2^\circ$ 2 θ .
9. Valacyclovir hydrochloride form II of claim 8 further characterized by x-ray diffraction reflections at about 9.2°, 15.6°, and 26.3° $\pm 0.2^\circ$ 2 θ .
10. Valacyclovir hydrochloride in form II of claim 8 further characterized as having an endothermic peak at about 214°C by differential thermal analysis.
- 20 11. Valacyclovir hydrochloride form II of claim 7 characterized by the x-ray diffraction pattern substantially as shown in figure 3.
12. Valacyclovir hydrochloride form IV.
13. Valacyclovir hydrochloride form IV of claim 12 characterized by the x-ray diffraction pattern substantially as shown in figure 6.

14. Valacyclovir hydrochloride form IV of claim 12 characterized by x-ray diffraction reflections at about 3.6°, 10.7°, 15.1°, 26.9°, and $28.1^\circ \pm 0.2^\circ 2\theta$.

15 Valacyclovir hydrochloride in form IV of claim 14 further characterized by x-ray diffraction reflections at about 7.2°, 8.6°, 9.5°, 13.3°, 15.2°, 27.3°, and $28.1^\circ \pm 0.2^\circ 2\theta$.

- 5 16. Valacyclovir hydrochloride form IV of claim 14 further characterized as having a water content between about 8% and about 11% as measured by thermogravimetric analysis over the temperature range between about 25° C and about 130° C.

17. Valacyclovir hydrochloride form V.

- 10 18. Valacyclovir hydrochloride in form V of claim 17 characterized by the x-ray diffraction pattern substantially as shown in figure 7.

19. Valacyclovir hydrochloride in form V of claim 17 characterized by x-ray diffraction reflections at about 6.7°, 15.7°, 16.2°, and $22.6^\circ \pm 0.2^\circ 2\theta$.

20. Valacyclovir hydrochloride in form V of claim 19 further characterized by additional x-ray diffraction reflections at about 3.4°, 9.5°, 13.5°, 21.9°, 27.2°, and $28.6^\circ \pm 0.2^\circ 2\theta$.

- 15 21. Valacyclovir hydrochloride in form V of claim 19 further characterized as having a weight loss of between about 5% and about 7% as measured by thermogravimetric analysis over the temperature range between about 25 °C and about 130 °C.

- 20 22. Valacyclovir hydrochloride in form V of claim 21 further characterized by a broad endothermic peak at about 95 °C and a sharp endothermic peak at about 180 °C in differential thermal analysis.

23. Valacyclovir hydrochloride in form VI.

24. Valacyclovir hydrochloride form VI of claim 23 characterized by the x-ray diffraction pattern substantially as shown in figure 9.

- 25 25. Valacyclovir hydrochloride in form VI of claim 23 characterized by x-ray diffraction reflections at about 6.2°, 9.2°, 12.1°, 20.2° and $25.7^\circ \pm 0.2^\circ 2\theta$.

26. Valacyclovir hydrochloride in form VII.

27. Valacyclovir hydrochloride form VII of claim 26 characterized by x-ray diffraction reflections at about 3.5° , 10.3° , 13.6° , 26.2° and $28.1^\circ \pm 0.2^\circ 2\theta$.

28. The valacyclovir hydrochloride in form VII of claim 26 characterized by the x-ray
5 diffraction pattern substantially as shown in figure 10.

29. A method of making valacyclovir hydrochloride form I comprising the step of slurring valacyclovir hydrochloride in a slurry solvent selected from the group consisting of ethyl acetate, acetone, methyl ethyl ketone, dioxane, methylene chloride, t-butyl methyl ether, and tetrahydrofuran.

10 30. The method of claim 29 further comprising the steps of:

isolating valacyclovir hydrochloride in form I from the slurry and

drying valacyclovir form I at a temperature between about 50°C and about 70°C .

15 31. A method of making valacyclovir hydrochloride form II comprising the step of slurring valacyclovir hydrochloride in a slurry solvent selected from the group consisting of isopropyl alcohol, 1-butanol, and ethanol.

32. The method of claim 28 wherein the slurry solvent is isopropyl alcohol.

33. A method of making valacyclovir hydrochloride form II comprising the steps of:
a, slurring valacyclovir in a slurry solvent selected from acetonitrile, methyl
20 ethyl ketone, ethyl acetate, acetone, and toluene

b, heating the slurry to reflux,

c, refluxing the resulting mixture, and

d, isolating valacyclovir hydrochloride in form II from the mixture.

34. The method of claim 33 wherein the slurry solvent is toluene and further comprising
25 the step of adding methanol to the refluxing mixture of valacyclovir hydrochloride and toluene.

35. The method of claim 34 further comprising the step of drying the isolated valacyclovir hydrochloride form II at a temperature of about 60°C.

36. The method of claim 32 further comprising the step of drying the isolated valacyclovir hydrochloride form II at a pressure less than about 500 mm Hg and the temperature is
5 about 50°C.

37. A method of making valacyclovir in form III comprising the step of incubating valacyclovir hydrochloride in an atmosphere saturated with vapors of at least one incubating solvent selected from the group consisting of isopropanol, ethanol, butanol, acetone, ethyl acetate, tetrahydrofurane, acetonitrile, and methanol.

10 38. The method of claim 37 wherein the valacyclovir hydrochloride is in solution in the incubating solvent.

39. The method of claim 37 wherein the valacyclovir hydrochloride is in solid form and the incubating solvent is acetonitrile.

15 40. A method of making valacyclovir hydrochloride form IV comprising the step of incubating valacyclovir hydrochloride in an atmosphere saturated with vapors of an incubating solvent that is water.

41. The method of claim 40 wherein the incubating solvent is water and the atmosphere has a relative humidity of about 100%.

20 42. A method of making valacyclovir hydrochloride in form V comprising the step of mixing a solution of valacyclovir hydrochloride in water with a lower aliphatic alcohol.

43. The method of claim 42 wherein the lower aliphatic alcohol is *iso*-propanol.

44. A method of making valacyclovir in form VI comprising the step of mixing a solution of valacyclovir hydrochloride in a first solvent comprising water and an aliphatic monocarboxylic acid, with a second solvent comprising a water-miscible ketone to form a
25 suspension.

45. The method of claim 44 wherein the first solvent comprises between about 30 % and about 60% by volume of water and wherein the amount of the second solvent is about 2 to about 5 times the volume of said first solvent.

46. The method of claim 44 wherein the water-miscible ketone is acetone.

5 47. The method of claim 44 further comprising the step of filtering the solution of valacyclovir hydrochloride in first solvent before the mixing step.

48. The method of claim 44 further comprising the steps of;

agitating the suspension at a temperature less than about -10° C and

isolating valacyclovir hydrochloride in form VI from the suspension.

10 49. A method of making valacyclovir in form VII comprising the step of mixing a solution of valacyclovir hydrochloride in a first solvent consisting essentially of water with a second solvent comprising a water-miscible ketone to form a suspension.

50. The method of claim 49 wherein the water-miscible ketone is acetone.

51. The method of claim 49 further comprising the steps of:

15 agitating the suspension at a temperature less than about -10° C; and

isolating valacyclovir hydrochloride in form VII from the suspension.

52. A method of making valacyclovir hydrochloride in form I comprising the steps of dissolving valacyclovir hydrochloride in a solvent, and evaporating the solution at a reduced pressure.

20 53. The method of claim 52 wherein the solvent is a polar organic solvent having 4 or fewer carbon atoms.

54. The method of claim 53 wherein the polar organic solvent is an alcohol.

55. The method of claim 54 wherein the solvent is methanol.

56. Valacyclovir hydrochloride monohydrate.

57. A method of making valacyclovir monohydrate comprising the step of contacting a solution of valacyclovir hydrochloride in water with iso-propanol to form a suspension.

58. The method of claim 57 wherein the contacting is at a temperature of between about 30°C and about 50°C.

59. The method of claim 58 wherein the contacting is at a temperature of about 40°C.

60. The method of claim 57 further comprising the steps of isolating the solid from the suspension and drying the isolated solid at a temperature of about 25°C to constant weight.

61. The method of claim 60 wherein the drying is at reduced pressure.

62. A pharmaceutical composition comprising at least one of valacyclovir hydrochloride in Forms I, II, IV, V, VI or VII.

63. The pharmaceutical composition of claim 53 further comprising at least one pharmaceutically acceptable excipient.

64. Valacyclovir hydrochloride dihydrate.